Postgraduate Medical Journal (February 1977) **53**, 78–81.

Angiokeratoma corporis diffusum: the evolution of a disease entity

A. TAAFFE
M.R.C.P.I., M.R.C.P.

Department of Dermatology, Cumberland Infirmary, Carlisle CA2 7HY

Summary

The clinical features, diagnosis, management, aetiology and inheritance of angiokeratoma corporis diffusum (Fabry's disease) are discussed and the literature reviewed. The treatment and knowledge generally of this rare condition have not greatly improved in 75 years.

Introduction

The original clinical descriptions of angiokeratoma corporis diffusum were published independently by Fabry in Germany and Anderson in London in 1898. Since then, discussion and research have expanded and explored many aspects of the disease—its clinical spectrum, mode of inheritance, histology and biochemistry. In the last 10 years, some attempts at treatment have been made.

Despite the constant trickle of publications on this condition and its allied sub-specialities, and its inclusion in all the major medical textbooks, physicians are still not as aware of it as they are of some other medical rarities. Delays in diagnosis are frequent and its clinical manifestations need constant reiteration.

The clinical features

The chief symptom of this condition is pain, and is evidenced by a characteristic eruption; a sex-linked mode of inheritance is usual. Increasing biochemical knowledge has increased the number of cases reported which do not fully comply with the criteria on which diagnosis was once based. However, as some of these patients are profoundly ill at the time of presentation, and as the correct diagnosis is often arrived at by a process of elimination, one suspects that vital clues in the personal or family history were not fully appreciated by the practitioners previously treating these patients.

The pains of Fabry's disease

These are often the earliest manifestation of the disease, frequently preceding the appearance of the eruption by months or years (De Groot, 1970). They are first felt at about the age of 9 years as a prolonged excruciating sensation at the tips of the fingers, the toes or the glans penis. They may affect the distal interphalangeal joints, the child being referred with a symmetrical peripheral arthritis causing him to stop his activities and cry. Misinterpretation is frequent, and the frequent association between the onset of the cramps and changes in environmental temperature may not be readily volunteered. This association (Wise, Wallace and Jellinek, 1972) is an important clinical clue. One child reported cramps in the early morning, but as these eased with the passage of the school day and the gradual rise of temperature, he was disbelieved by his parents, teachers and doctor (De Groot, 1970). Three years elapsed before the appearance of the eruption.

One case of ophthalmic zoster was less painful than the concomitant Fabry's disease (Wise *et al.*, 1962). Another patient in the same series had penile pains unrelated to erection. He was subsequently reviewed in his terminal illness when he had constant, intractable genital pain (Steward and Hitchcock, 1968). One patient, with abdominal cramps as presenting complaint, was reported by Urbain, Phillipart and Peremans (1969). The surgeon can be faced with a similar dilemma when abdominal pains sometimes occur in neurosyphilis. A patient is reported who had peripheral cramps and also required laparotomy to exclude a second disease as the cause of right upper quadrant pain (von Gemmingen, Kierland and Opitz, 1965). Four cases subjected to surgery for lower abdominal pain were found to have normal vermiform appendices (Rahman and Lindberg, 1963).

The eruption

Although asymptomatic, the eruption is of primary clinical importance. The patient's age at its or set varies but it usually appears early in the second decade. The lesions, usually less than 2 mm in diameter, are dark red and not unlike the flecks of altered blood seen near any minor abrasion. They are found mainly singly or in groups on the lower half of the body. The nail beds are seldom involved,

Present address: Department of Dermatology, University Hospital of Wales, Cardiff.

and no lesions of the head or neck were noted by Wise *et al.* (1962) in twenty-one cases, nor among the cases reported by others before this time.

The lesions may be found in clusters over the hip joints or concentrated around the umbilical brim forming a characteristic rosette. Occasional lesions are seen on the glans penis, on the mucosal lining of the buccal cavity, the lips, or the conjunctiva concealed by the lower lids (Wise *et al.*, 1962). The lesions are not haemorrhagic as a rule.

The eyes

The eyes may be affected in several ways. There may be inward-pointing triangular opacities studding the cornea (like a Maltese cross in appearance); the exact slit-lamp technique required to see these lesions was described by Von Gemmingen *et al.* (1965) whose paper also featured a photograph of the dilated serpiginous veins of the optic fundi which are peculiar to this disease. A chloroquine-type keratopathy has also been described (Wise *et al.*, 1962). In the terminal stage of the illness, hypertensive or uraemic retinal changes supervene on the pre-existing lesions of Fabry's disease.

The cardiovascular system

In addition to the telangiectatic appearance of the skin, the cardiovascular system may be otherwise affected. The symptoms and signs of cardiac involvement are often subtle and difficult to define. They may be insidious in onset and clinical assessment is often thwarted by uraemic hypervolaemia, hypertension, which in Fabry's may be caused by chronic renal failure, or anaemia secondary to involvement of the bone marrow. Thus an apical systolic murmur radiating to the axilla may have a variety of aetiologies. Nevertheless, cardiac involvement is often the dominant lesion with or without the other haemodynamic influences. Angina pectoris, myocardial infarction, and electrocardiographic conduction defects are cited in nearly every series reported and, in one case, the possibility of specific involvement of the mitral valve was discussed (Ferrans, Hibbs and Burda, 1969).

The central nervous system

Pre-senile dementia, vertigo due to damage of the sensory nucleus of the V cranial nerve, myoclonic seizures and pontine haemorrhages have all been described (Steward and Hitchcock, 1968). It is postulated that the episodic pyrexia found in the early stages of some cases of the disease can be explained by the discovery of small haemorrhages or infarcts in the paraventricular or preoptic nuclei of the brain (Rahman and Lindenberg, 1963). The now well established involvement of the autonomic nervous system does not fully account for the cause of the cramps in these patients, although it helps to explain the diarrhoea (Steward and Hitchcock, 1968; Rahman and Lindberg, 1963; Urbain *et al.*, 1969) and disturbances of normal sweating responses.

The renal involvement

This is the most serious complication of the disease. It begins at the end of the second decade of the disease and further compounds the other manifestations with hypertension and hypervolaemia.

In the series of twenty-one cases reported by Wise *et al.* (1962), eighteen patients had hypertension, proteinuria or an abnormal urinary specific gravity. In another series (Von Gemmingen *et al.*, 1965), four out of eight patients had clinical evidence of renal impairment; a case has been reported of Fabry's disease presenting as renal failure but lacking the other stigmata of the condition (Clarke *et al.*, 1972).

The clinical diagnosis

Early diagnosis is of paramount importance. Once seen, the cutaneous lesions are not easily forgotten. However, cases are rare and the condition is in danger of being considered 'a rare diagnostic rubric' (Brady *et al.*, 1967) and it is not surprising that ignorance remains the chief cause of delay in reaching a diagnosis (Wise *et al.*, 1962; De Groot, 1970). The following conditions are included within the scope of the differential diagnosis:

Angiokeratoma of Fordyce. This condition is characterized by the appearance of small bright red papules on the scrotum in adolescence. Although the density of pigmentation of the lesions increases with age, these are not associated with systemic illness nor do they spread beyond the scrotum.

Angiokeratoma of Mibelli. The lesions in this condition may measure 5 mm in diameter, and are usually found on the lateral aspects of the fingers and toes. The co-existence of a chilblain circulation is the main clinical clue.

Hereditary haemorrhagic telangiectasia. In this condition (also known as Sutton-Rendu-Osler-Weber syndrome), haemorrhage may lead to severe iron-deficiency anaemia. Lesions in the lungs can be sufficiently severe to cause shunts in the lesser circulation and secondary polycytaemia in the blood stream (Harrington, Beeson and McDermott, 1969).

The growth of understanding

The early reports concentrated on morphology, nomenclature and classification. Fabry named the condition 'angiokeratoma corporis diffusum' but Anderson, also writing in 1898, reported proteinuria and postulated a generalized, systemic condition possibly due to diffuse vascular disease. Further cases were reported by different observers and

Madden (1912) reported a case which was at first mistaken for schistosomiasis. This patient was seen by Sir William Osler, then in Egypt, who confessed to never having seen such a case. As late as 1943, Parkes Weber published a list of twenty common telangiectatic conditions but Fabry's disease was not one of them.

The concept of a lipid storage disease

Many of the earlier reported cases were carefully followed-up by the original authors. The incidence of uraemia and hypertension was noted and studies of post-mortem material by Ruiter, Pompen and Wijers (1947) led to the suggestion of lipid storage disease. However, the source of this lipid remained undetermined.

The mode of inheritance

Reviewing the literature, Wise *et al.* found there had been forty cases reported up to 1958. All of these were male, as were all but one of their own series (Wise *et al.*, 1962). This series was then the most comprehensive study published and is still the most useful source of reference for students of the condition, and serves as the best available publication for detailed clinical information. These authors concluded that the mode of inheritance must be sex-linked.

The following are generalizations useful in genetic counselling (Von Gemmingen *et al.*, 1965): (1) Unless there has been a new mutation, the patient has inherited his disease through his mother; (2) corneal dystrophies almost always occur in the female carrier, a useful sign for carrier screening; (3) there is no inheritance from the affected male to his sons but there is to his daughters; (4) the carrier female will probably transmit the defect to half her sons and half her daughters assuming a 50% ratio in the sex of the children.

The nature of the lipid

Evidence that the abnormal glycolipid was ceramidetrihexoside, was advanced by Sweeley and Klionsky (1963). They identified their glycolipid in renal tissue. Further demonstrations of such material in the spleen and lymph nodes and Meissner's plexus were made by Urbain *et al.* (1969). Extensive cardiac infiltration was demonstrated by Ferrans *et al.* (1969) and they confirmed that the angiokeratomata were in fact areas of ectasia of blood vessels caused by lipid damage to their walls. As early as 1963 Rahman and Lindenberg had demonstrated that although specific infiltration of certain areas of the nervous system occurred, the commonest cause of neurological damage in Fabry's disease was the lipid infiltration of the cerebral vasculature.

The source of the abnormal lipid

Brady *et al.* (1967) discovered a deficiency of α-galactosidase, an acid hydrolase which removes hexose molecules from complex glycolipids, thereby preventing the hydrolysis of ceramidetrihexoside to ceramidihexoside and galactose. Thus, there is an excess of ceramidetrihexoside causing a biochemical state analogous to Gaucher's disease. Demonstration of α-galactosidase deficiency in the lysosomes of many tissues of the body was made by Kint (1970).

The treatment of Fabry's disease

Until recently, the most important reasons for making an early diagnosis of this affliction were genetic counselling and the management of pain. There is very little written about the correct choice of analgesics. Individual clinicians suggest carbamazepine on an empirical basis and with the rapid rate of research into the disease it seems reasonable to restrict the use of opiate analgesics to those who are crippled with pain and have multi-system involvement. In recent years two exciting forms of therapy have been suggested.

(i) *Replacement of the missing enzyme by infusion therapy.* This was tried using two separate sources of enzyme, fresh plasma and purified extract of human placental tissue, infusing each into one of two patients (Brady *et al.*, 1973). In both patients there was a reduction of circulating ceramidetrihexoside levels which lasted for about 48 hr although there was no reduction of the urinary levels. A rapid concentration of the infused enzyme occurred in the liver of the recipients even before there was any decline in the level of circulating glycolipid. This suggested that the liver is the site of ceramidetrihexoside metabolism in normal people.

The plasma as a source of enzyme has a disadvantage in that relatively large volumes of fluid have to be used on the patient, with a possible risk of renal failure. The authors argue that the use of fresh leucocytes and platelets as a source of enzymes presents problems of compatibility. They feel that the placental extract as a source of exogenous enzyme is likely to create difficulties of antigenicity but to date is the vehicle of choice.

(ii) *Enzyme replacement by renal allograft transplantation.* Krivit *et al.* (1972) recorded nine renal transplants for patients with this condition. Four of these were successful, the symptoms of Fabry's disease had subsided and the urinary and plasma ceramidetrihexoside levels had returned to normal. Furthermore, the α-galactoside levels had been brought up to normal.

The theoretical advantages of renal transplantation have been promulgated by Clarke *et al.* (1972) and may be summarized as follows: (a) since the progression of the disease is slow, the relatively small

amount of tissue contributed by the graft should be sufficient to metabolize the excess ceramidetrihexoside; (b) the fact that the blood vessels are the tissues most seriously infiltrated with the abnormal glycolipid suggests that the degree of infiltration is proportional to chronically elevated glycolipid levels and the process should be arrested if the circulating levels are reduced; (c) since the terminal event is renal failure, renal transplant offers a means of both enzyme replacement and correction of the renal failure.

Conclusion

Renal failure, the terminal event, can now be treated by renal transplantation but the question is whether the other attribute of renal transplantation, enzyme replacement, justifies this form of treatment as a prophylactic procedure. It is tragic that after 75 years our understanding of the cause of pain in this condition, or indeed the best form of its treatment, is little better than that of the original authors in 1898.

Acknowledgment

I wish to thank Col. P. C. Mitchell, T.D., M.B., F.R.C.P. for his encouragement to publish.

References

ANDERSON, W. (1898) A case of 'angiokeratoma'. *British Journal of Dermatology*, **10**, 113.

BRADY, R.O., GAL, A.E., BRADLEY, R.M., MARTENSSON, E., MARSHAW, A.L. & LASTER, L. (1967) Enzymatic defect in Fabry's disease. *New England Journal of Medicine*, **276**, 1163.

BRADY, R.O., TALLMAN, J.F., JOHNSON, W.G., GAL, A.E., LEAHY, W.R., QUIRK, J.M. & DEKHVAN, A.S. (1973) Replacement therapy for inherited enzyme deficiency (use of purified ceramidetrihexoside in Fabry's disease). *New England Journal of Medicine*, **289**, 9.

CLARKE, J.T.R., GUTTMAN, R.D., WOLFE, L.S., BEAUDOIN, J.G. & MOORHOUSE, D.D. (1972) Enzyme replacement therapy by renal allotransplantation in Fabry's disease *New England Journal of Medicine*, **287**, 1215.

FABRY, J. (1898) Ein Beitrag zur Kenntnis der Purpura haemorragica (Purpura papulosa haemorrhagica hebra). *Archiv für Dermatologie und Syphilis*, **43**, 187.

FERRANS, V.J., HIBBS, R.G. & BURDA, C.D. (1969) The heart in Fabry's disease—a histochemical and electron microscopic study. *American Journal of Cardiology*, **24**, 95.

GROOT, W.P. DE (1970) Fabry's disease in children. *British Journal of Dermatology*, **82**, 329.

HARRINGTON, M.J., BEESON, P. & MCDERMOTT, W. (1967) *Textbook of Medicine*, 12th Edn, p. 1123. W. B. Saunders Company, Philadelphia.

KINT, J.A. (1970) Fabry's disease alpha-galactosidase-deficiency. *Science*, **167**, 1268.

KRIVIT, W., DESSNICK, R.J., BERNLOHR, R.W., WOLD, F. NEJARIAN, J.S. & SIMONS, R.L. (1972) Enzyme transplantation in Fabry's disease. *New England Journal of Medicine*, **287**, 1248.

MADDEN, F.C. (1912) Papilliform lesions (lymphangiomata) of the scrotum. *British Medical Journal*, **2**, 302.

PARKES WEBER, F. (1943) Some telangiectatic and other anomalous vascular groups, especially those of diplastic origin. *The Medical Press and Circular*, **210**, 219.

RAHMAN, A.N. & LINDENBERG, R. (1963) The neuropathology of hereditary dystrophic lipidosis. *Archives of Neurology*, **9**, 373.

RUITER, M., POMPEN, A.W.M. & WIJERS, H.J.G. (1947) Über interne und pathologisch-anatomische Befunde bei Angiokeratoma Corporis diffusum (Fabry). *Dermatologica*, **94**, 1.

STEWARD, J.M. & HITCHOCK, C. (1968) Fabry's disease—a report of five cases with pain in the extremities as the chief symptoms. *Pathologia europaea*, **3**, 373.

SWEELEY, C.C. & KLIONSKY, B. (1963) Fabry's disease: classification as a sphingolipidosis and partial characterization of a novel glycolipid. *Journal of Biological Chemistry*, **238**, 3148.

URBAIN, G., PHILLIPART, M. & PEREMANS, J. (1969) Fabry's disease with hypogammaglobulinemia and without angiokeratoma. *Archives of Internal Medicine*, **124**, 72.

VON GEMMINGEN, G., KIERLAND, R. & OPITZ, J.M. (1965) Angiokeratoma coporis diffusum. *Archives of Dermatology*, **91**, 206.

WISE, D., WALLACE, H.J. & JELLINEK, E.H. (1962) Angiokeratoma corporis diffusum—clinical study of eight affected families. *Quarterly Journal of Medicine*, **31**, 177.